

Pericardial Disease

Cardiac Troponin I in Acute Pericarditis

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OBJECTIVES	This study was designed to investigate the prognostic value of cardiac troponin I (cTnI) in viral or idiopathic pericarditis.
BACKGROUND	Idiopathic acute pericarditis has been recently reported as a possible cause of nonischemic release of cTnI. The prognostic value of this observation remains unknown.
METHODS	We enrolled 118 consecutive cases (age 49.2 ± 18.4 years; 61 men) within 24 h of symptoms onset. A highly sensitive enzymeimmunoassay method was used to measure cTnI (acute myocardial infarction [AMI] threshold was 1.5 ng/ml).
RESULTS	A cTnI rise was detectable in 38 patients (32.2%). The following characteristics were more frequently associated with a positive cTnI test: younger age ($p < 0.001$), male gender ($p = 0.007$), ST-segment elevation ($p < 0.001$), and pericardial effusion ($p = 0.007$) at presentation. An increase beyond AMI threshold was present in nine cases (7.6%), with an associated creatine kinase-MB elevation, a release pattern similar to AMI, and echocardiographic diffuse or localized abnormal left ventricular wall motion without detectable coronary artery disease. After a mean follow-up of 24 months a similar rate of complications was found in patients with a positive or a negative cTnI test (recurrent pericarditis: 18.4 vs. 18.8%; constrictive pericarditis: 0 vs. 1.3%, for all $p = \text{NS}$; no cases of cardiac tamponade or residual left ventricular dysfunction were detected).
CONCLUSIONS	In viral or idiopathic acute pericarditis cTnI elevation is frequently observed and commonly associated with young age, male gender, ST-segment elevation, and pericardial effusion at presentation. cTnI increase is roughly related to the extent of myocardial inflammatory involvement and, unlike acute coronary syndromes, is not a negative prognostic marker. (J Am Coll Cardiol 2003;42:2144–8) © 2003 by the American College of Cardiology Foundation

Troponins I and T are regulatory proteins that control the calcium-mediated interaction of actin and myosin (1). The cardiac forms of these proteins are products of specific genes and therefore have the potential to be unique for the heart. Studies performed with cardiac troponin I (cTnI), the cardiac muscle isoform of troponin I, have failed to find any cTnI outside of the heart at any stage of neonatal development (2,3); moreover, an increase in cTnI circulating levels is highly indicative of myocardium injury (2).

Cardiac troponin I has been extensively studied as a diagnostic and prognostic marker in acute coronary syndromes, and recent studies have demonstrated increased circulating levels in conditions with myocardial injury different from coronary heart disease (4–6).

The inflammatory process of acute pericarditis may involve the epicardium and cause myocardial damage, as reflected by creatine kinase (CK)-MB enzyme release (7). This damage may be also responsible for cTnI release in patients with acute pericarditis, as recently reported (8,9). The temporal pattern of this release is similar to that of an acute myocardial infarction (AMI); however, the true prog-

nostic significance of cTnI remains unknown in this setting (8,9).

The aim of this work is to investigate the clinical and prognostic value of cTnI release in patients with viral or idiopathic acute pericarditis.

METHODS

Patients. This study was performed with the approval of the institutional review board and subjects gave informed consent. From January 2000 to January 2002 we prospectively studied all consecutive cases of acute pericarditis admitted to the Emergency Department or our Cardiology Department (including ambulatory and day hospital service) within 24 h of symptom onset. Acute pericarditis was diagnosed with at least two of the following criteria: pericarditic chest pain, pericardial friction rub, and widespread ST-segment elevation on the electrocardiogram (ECG). A complete echocardiographic study was performed in all patients using a Hewlett-Packard 2500 or 5500 machine (Palo Alto, California). Initial evaluation included ECG, chest X-ray, and routine laboratory tests (blood cell count, sedimentation rate, acute phase reactants, serum urea, and creatinine) as well as antinuclear antibody titers, rheumatoid factor, tuberculin skin test, human immunodeficiency virus serology, and, if the patient was febrile, blood cultures. Appropriate studies were performed if initial eval-

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CK = creatine kinase
cTnI = cardiac troponin I
ECG = electrocardiogram

uation suggested a specific cause, such as tuberculosis or malignancy. We did not routinely obtain viral studies, because the yield is low and management is not altered by viral serology results. In the future this approach may change with the introduction into clinical practice of new treatments for specific viral infections. Pericardiocentesis was performed in patients with cardiac tamponade, suspected purulent pericarditis, clinical activity, or effusion persisting for more than one week after aspirin therapy. Surgical drainage and pericardial biopsy were limited to relapses of cardiac tamponade after pericardiocentesis or cases with persistent illness for more than three weeks without evident etiology. Institution of antituberculosis therapy was performed if the diagnosis of tuberculous pericarditis was established (10,11).

To avoid confounding effects of different secondary etiologies with an unfavorable prognosis (such as tumor), only viral or idiopathic acute pericarditis cases were included in the study after exclusion of secondary causes (including tumors, connective tissue disease, tuberculous pericarditis, and other discernible etiologies).

Patients with viral or idiopathic acute pericarditis were treated with aspirin (800 mg orally every 6 or 8 h for 7 to 10 days with gradual tapering over 2 to 3 weeks) and gastroprotection with misoprostol (600 to 800 μ g daily) or omeprazole (20 mg daily).

A clinical and echocardiographic follow-up was performed at 48 to 72 h, 7 to 10 days, 1 month, 6 months, and 1 year and then yearly in noncomplicated cases.

cTnI and CK-MB assays. Venous blood for determination of cTnI, CK-MB fraction was collected on dry tubes from an antecubital vein. The cTnI was measured using a Dade Behring Flex reagent cartridge (Deerfield, Illinois), based on a highly sensitive enzymoimmunoassay method with a lowest measurable concentration of 0.04 ng/ml, reference interval: 0 to 0.1 ng/ml and an AMI threshold: of 1.5 ng/ml). The CK-MB enzyme release was measured using Dade Behring Flex reagent for CK-MB, an immunoinhibition assay (lowest measurable concentration of 1.0 U/l, reference interval <6 ng/ml). The cTnI and CK-MB assays performances were according to the European Society of Cardiology and American College of Cardiology consensus document (12). All patients had serial cTnI measurements independently from the first assay result to exclude a late cTnI rise.

An acute coronary syndrome was excluded as a possible etiology for cTnI elevation. All patients with a cTnI assay beyond AMI threshold underwent coronary angiography to

Table 1. Clinical, Electrocardiographic, and Echocardiographic Findings in Patients With Viral or Idiopathic Acute Pericarditis With and Without Detectable cTnI

	Serum cTnI (ng/ml) (n = 118)		p Value
	≤ 0.1 (n = 80)	> 0.1 (n = 38)	
Age (yrs)	57.3 \pm 15.1	31.9 \pm 11.4	<0.001
Male gender	34 (42.5)	27 (71.0)	0.007
Pericardial friction rub	29 (36.2)	11 (28.9)	NS
ST-segment elevation	45 (56.2)	37 (97.4)	<0.001
Pericardial effusion	48 (60.0)	33 (86.8)	0.007
Erythrocyte sedimentation (mm)	34 \pm 30	38 \pm 28	NS
C-reactive protein (mg/ml)	70 \pm 50	80 \pm 40	NS
White blood count (10^3 /ml)	11 \pm 4	12 \pm 3	NS

Mean \pm standard deviation or number of cases (percentage).

cTnI = cardiac troponin I.

exclude coronary artery disease (CAD) or coronary artery spasm by ergonovine test. Other patients with a positive cTnI test below AMI threshold underwent functional tests (exercise ECG or stress echocardiography) to exclude CAD. **Statistical analysis.** Data were expressed as mean \pm SD. Comparison between patient groups were performed using unpaired *t* test for continuous variables and a chi-square analysis for categorical variables. Correlations between cTnI and CK-MB levels were calculated by Spearman correlation. A p value of <0.05 was considered to show statistical significance.

RESULTS

Patients. A total of 118 consecutive cases of viral or idiopathic acute pericarditis (80.5% of all cases presenting with acute pericarditis) were included within 24 h of symptoms onset. Mean age was 49.2 \pm 18.4 with 61 men (51.7%). Fever was present in 59 cases (50.0%), pericardial friction rubs in 40 cases (33.8%), and ST-segment elevation in 82 cases (69.5%), with a typical ECG evolution in 65 cases (55.1%). PR-segment depression was recorded in 90 cases (76.3%) and was associated with ST-segment elevation in 59 cases (50.0%). A pericardial effusion was detected in 71 cases (60.2%); in all cases the effusion was small with a good response to medical therapy. According to our study protocol we did not perform pericardiocentesis or any diagnostic work on pericardial fluid in these cases. Echocardiographic diffuse or localized abnormal ventricular wall motion was recorded in nine cases (7.6%).

cTnI and CK-MB values. A cTnI rise was detectable in 38 patients (32.2% of cases). The mean cTnI value was 1.02 \pm 1.21 ng/ml (range 0.2 to 28.0 ng/ml).

The ST-segment elevation was observed in almost all cases with a detectable cTnI (37/38; 97.4%). Sensitivity of ST-segment elevation to detect important myocardial injury (cTnI ≥ 1.5 ng/ml) was 88.9%, but its specificity was only 32.1%. This sensitivity was improved to 100% by concomitant PR-segment depression.

The following characteristics (Table 1) were more fre-

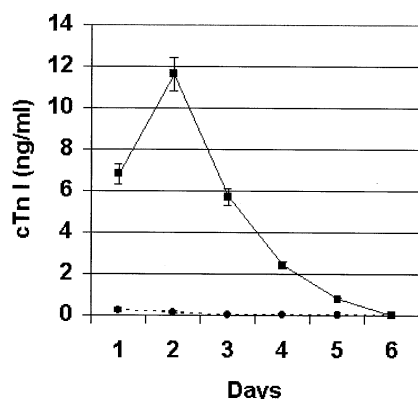


Figure 1. Temporal changes of cardiac troponin I (cTnI) in viral or idiopathic acute pericarditis. In group II (solid line, squares) cTnI temporal pattern was similar to that seen in acute myocardial infarction with levels detectable for 5 to 6 days while in group I (dashed line, circles) cTnI temporal pattern was shorter (2 to 3 days). Data are expressed as means \pm standard deviations from 29 patients in group I and from nine patients in group II.

quently associated with a positive cTnI test: younger age (31.9 ± 11.4 years vs. 57.3 ± 15.1 years, $p < 0.001$), male gender (71% vs. 42.5%, $p = 0.007$), ST-segment elevation (97.4% vs. 56.2%, $p < 0.001$) and pericardial effusion at presentation (86.8% vs. 60.0%, $p = 0.007$). Among patients with a positive cTnI test a mild increase of cTnI (<0.4 ng/ml) was detected in 29 cases (group I: 24.6% of all) without CK-MB elevation. An increase beyond AMI threshold was present in nine cases with an associated CK-MB elevation and echocardiographic diffuse or localized abnormal left ventricular wall motion (group II: 7.6% of all patient and 23.7% of positive cTnI cases; mean cTnI: 11.6 ± 7.8 ng/ml; mean CK-MB peak 23.6 ± 19.0 U/l). There was a significant correlation between cTnI and CK-MB values ($r = 0.60$; $p < 0.05$). In these cases CAD was excluded by angiography and myopericarditis was diagnosed. In group II cTnI temporal pattern was similar to that seen in AMI with levels detectable for five to six days, whereas in group I the temporal pattern was shorter (2 to 3 days) (Fig. 1).

According to our study protocol initial routine treatment was the same in all patients, and there were no differences in treatment between patients with a positive or a negative cTnI test. A mean follow-up of 24 months (range 8 to 30 months) was performed. A similar rate of complications (Table 2) was found in patients with a positive or a negative cTnI test (recurrent pericarditis: 18.4% vs. 18.7%; constrictive pericarditis: 0 vs. 1.3%, for all $p = \text{NS}$; no cases of cardiac tamponade or residual left ventricular dysfunction were detected). A complete regression of left ventricular regional wall motion abnormalities was documented in all patients in group II with recovery.

DISCUSSION

Major findings. Elevations of cTnI levels have been observed across a spectrum of acute coronary syndromes

Table 2. Complications and Clinical Events During a Mean Follow-Up of 24 Months (Range 8 to 30 Months)

	Serum cTnI (ng/ml) (n = 118)		p Value
	≤ 0.1 (n = 80)	> 0.1 (n = 38)	
Recurrent pericarditis	15 (18.8%)	7 (18.4%)	NS
Cardiac tamponade	0	0	NS
Constrictive pericarditis	1 (1.3%)	0	NS
Residual left ventricular dysfunction	0	0	NS
Congestive heart failure	0	0	NS
Dilated cardiomyopathy	0	0	NS

cTnI = cardiac troponin I.

including Q-wave MI, non-Q-wave MI, and unstable angina. At present, troponins are the primary biochemical tests for the diagnosis of AMI (12). Moreover cTnI has been extensively studied as a prognostic marker in acute coronary syndromes: the prognostic value of elevated serum troponins has been demonstrated in patients with unstable angina and both non-Q-wave and Q-wave myocardial infarction (13–15).

Several studies have also demonstrated increased circulating levels of cTnI in conditions with myocardial injury different from coronary heart disease, such as congestive heart failure, myocarditis, and pulmonary embolism (4–6). Recently increased serum levels of cTnI have been reported in idiopathic acute pericarditis (8,9).

In the first report (8), a retrospective monocentric study, 69 hospitalized patients were included after review of the emergency department and hospital databases. In this study serum cTnI was detected on admission in 34 patients (49% of cases) and was beyond the AMI threshold in 15 cases (22%). The cTnI increase was seen almost only in patients with ST-segment elevation. Patients with higher values of cTnI were younger and had a recent infection.

In the second observational report (9), 14 patients with idiopathic acute pericarditis were enrolled at admission to the emergency department within 24 h of symptom onset.

The cTnI elevation was observed in 10 cases (71%). In this study cTnI levels were detectable for a maximum of six days and with a temporal pattern similar to that observed in AMI. The prognostic value of this observation was not investigated.

In these studies serum cTnI elevation was not related to symptom intensity or disease severity, and the prognostic significance of the observation was not investigated prospectively.

To the present our study is the largest report of serum cTnI elevation in viral or idiopathic acute pericarditis, and the first prospective one to evaluate its clinical and prognostic value. The cTnI was evaluated at admission within 24 h of symptom onset and later every 6 h for one day and then daily. We observed an increase of serum cTnI in only 32.2% of cases, with a value that was above AMI threshold (1.5 ng/ml) in 7.6% of cases. A positive cTnI test was

Table 3. cTnI Elevation in Viral or Idiopathic Acute Pericarditis: Comparison Between This Report and Previous Studies

Study	Years (Printed)	Study Design	Setting	Patients	cTnI Assay	cTnI+	cTnI+ (≥ 1.5 ng/ml)
Bonnefoy et al. (8)	1996–1997 (2000)	Monocentric Retrospective	Hospital	69	Dade, Stratus	34 (49%)	15 (22%)
Brandt et al. (9)	1998–1999 (2001)	Monocentric Observational	Hospital	14	Abbott Lab	10 (71%)	n.d.
Imazio et al.	2000–2002 (2003)	Monocentric Prospective	Hospital Day hospital Ambulatory	118	Dade, Stratus	38 (32%)	9 (7.6%)

cTnI = cardiac troponin I; n.d. = not determined.

associated with younger age, male gender, ST-segment elevation, and pericardial effusion at presentation (for all $p < 0.01$). Moreover, we observed that the highest values of cTnI (≥ 1.5 ng/ml) were associated with CK-MB elevation and echocardiographic wall motion abnormalities; in these cases CAD was excluded by coronary angiography and myopericarditis was diagnosed. The longer time period of elevated cTnI levels in group II was probably the result of a more severe myocardial involvement.

In our experience the entity of serum cTnI elevation is roughly related to disease severity, probably reflecting the extent of inflammatory and degenerative changes of the superficial myocardium.

Moreover, related to the severity of the disease, we observed two different temporal patterns of cTnI release. The most frequent pattern of cTnI release was observed in 24.6% of all cases with a mild increase of serum cTnI (≤ 0.4 ng/ml) without CK-MB elevation lasting for < 3 days (Fig. 1). Higher values of cTnI (≥ 1.5 ng/ml) were observed in 7.6% of all cases together with CK-MB elevation, echocardiographic wall motion abnormalities, and a prolonged pattern similar to that observed in AMI (Fig. 1). Despite different temporal patterns, we found a similar rate of complications in patients with a positive (independently from cTnI peak levels) or a negative cTnI test.

In comparison with previous studies we observed a less frequent cTnI release in idiopathic acute pericarditis: only 32.2% of cases compared with 49% to 71% of reported studies (8,9). These differences can be explained considering different study design, setting, sample size and cTnI assays (Table 3).

In the present study, 118 consecutive patients with viral or idiopathic acute pericarditis were enrolled in a prospective study, including hospitalized patients and patients treated on an ambulatory or day hospital basis. Hospitalized patients are generally clinically more severe to require hospitalization; thus, patient preselection cannot be excluded in previous studies and could be responsible for an overrating of cases with a positive cTnI test.

Study limitations. If cTnI elevation reflects more extensive acute myocardial inflammation and injury, then one might expect that a positive value would carry prognostic significance. However, the pathophysiologic process leading to cTnI release in myopericarditis is distinctly different from that in patients with acute coronary syndromes, and it is

uncertain whether a cTnI elevation carries the same prognostic value. Acute pericarditis etiologies are diverse, and prognosis may be related more to the underlying illness than the presence or absence of troponin release (16). In this study only viral or idiopathic cases of acute pericarditis were studied.

It is generally known based on dated previous reports (10,11) that idiopathic acute pericarditis can have a good prognosis therefore it would seem unlikely that cTnI is able to predict poor prognosis in patients with viral or idiopathic acute pericarditis, however this hypothesis has not been formally tested in a prospective study. Recent papers reported cTnI release in patients with idiopathic acute pericarditis, sometimes with a temporal pattern similar to that of an AMI, but the true prognostic significance of these observations remain unknown in this setting (8,9). To the present, even if it is a single-center observational study, this report represents the largest series of patients with viral or idiopathic acute pericarditis evaluated for markers of myocardial injury.

Conclusions. The cTnI elevation is not rare in viral or idiopathic acute pericarditis, but is less frequent than previously reported, and is probably the biochemical evidence of myocardial inflammatory damage. It is associated with young age, male gender, ST-segment elevation, and pericardial effusion at presentation and is roughly related to the disease severity, probably reflecting the extent of inflammatory and degenerative changes of the superficial myocardium, with the highest values generally observed during myopericarditis. Unlike acute coronary syndromes, cTnI is not a negative prognostic marker in viral or idiopathic acute pericarditis.

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REFERENCES

- Adams JE, Abendschein DR, Jaffe AS. Biochemical markers of myocardial injury. Is MB creatine kinase the choice for the 1990s? *Circulation* 1993;88:750–63.
- Adams JE, Bodor GS, Davilla-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation* 1993; 88:101–6.

3. Bodor GS, Porterfield D, Voss EM, et al. Cardiac troponin I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. *Clin Chem* 1995;41:1710–5.
4. Missov E, Calzolari C, Pau B. Circulating cardiac troponin I in severe congestive failure. *Circulation* 1997;96:2953–8.
5. Lauer B, Niederau C, Kühl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. *J Am Coll Cardiol* 1997;30:1354–9.
6. Douketis JD, Crowther MA, Stanton EB, et al. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. *Arch Intern Med* 2002;162:79–81.
7. Karajalainen J, Heikkilä J. Acute pericarditis: myocardial enzyme release as evidence for myocarditis. *Am Heart J* 1986;111:546–52.
8. Bonnefoy E, Godon P, Kirkorian G, et al. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. *Eur Heart J* 2000;21:832–6.
9. Brandt RR, Filzmaier K, Hanrath P. Circulating cardiac troponin I in acute pericarditis. *Am J Cardiol* 2001;87:1326–8.
10. Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol* 1985;56:623–30.
11. Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. *Am J Cardiol* 1995;75:378–82.
12. Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000;36:959–69.
13. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac specific troponin-I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342–9.
14. Ohman EM, Armstrong PW, White HD, et al. Risk stratification with a point-of-care cardiac troponin T test in acute myocardial infarction. GUSTO III Investigators. Global Use of Strategies To Open Occluded Coronary Arteries. *Am J Cardiol* 1999;84:1281–6.
15. Ottani F, Galvani M, Nicolini FA, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J* 2000;140:917–27.
16. Hamm CW, Giannitsis E, Katus HA. Cardiac troponin elevations in patients without acute coronary syndrome. *Circulation* 2002;106:2871–2.